Attorney Docket No. P60953US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: JENSEN et al.

#25
6/21/03

Application No.: 09/060,294 Art Unit: 1646

Filed: April 15, 1998 Examiner: D. ROMEO

For MODIFIED TNF-α MOLECULES, DNA ENCODING SUCH AND VACCINES COMPRISING SUCH MODIFIED TNF-α AND DNA

SUPPLEMENT TO AMENDMENT

Mail Stop Non-Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The instant paper supplements the preliminary Amendment (CPA) filed March 4, 2002.

In order to better address the issues raised in the §103(a) rejection of record, the instant remarks focus on one of the salient features of the presently claimed invention, namely, that the antibodies induced by the modified TNF-alpha molecules must be neutralizing *per se*. This feature (limitation) of the instant claims is neither taught nor suggested in WO95/05849 (Mouritsen).

Following the teaching from Mouritsen concerning modification of TNF-alpha, in order to obtain biologically inactive molecules, which may induce autoantibodies, one skilled in the art would end up with a modified human TNF-alpha, such as TNF2-1. According to Example 4, TNF2-1 induces antibodies against human TNF-alpha, as would have been expected from Mouritsen.

However, the presently claimed invention focuses on the ability of the induced antibodies to neutralize, very quickly, the effect of native TNF-alpha at local high concentrations, for example, in connection with a local inflammation. In accordance with the presently claimed invention, it is

not enough that the induced antibodies only initiate the normal cascade of elimination via macrophages, which takes a long time. If an immediate neutralization is needed, the antibodies have to be neutralizing, *per se*. As shown in present Example 4, it turned out that TNF2-1, the modified human TNF-alpha following from the teaching of Mouritsen, does not induce antibodies with a neutralizing effect. The teaching of Mouritsen would not, therefore, have lead one skilled in the art to the modified human TNF-alpha having the desired properties in accordance with presently claimed invention.

In order to obtain neutralizing antibodies, the active site should, in theory, be preserved in the inducing antigen, i.e., the modified TNF-alpha. By using biologically active TNF-alpha, the chance of obtaining neutralizing antibodies is high, compared to using TNF-alpha modified at the active site as the inducing antigen, since the neutralizing antibody needs to recognize, and bind at, the active site in the native TNF-alpha, in order to execute its neutralizing effect. However, because of toxicity it is not possible in practice to use biologically active TNF-alpha as the antigen. A modification of the active site would greatly diminish the chance of obtaining neutralizing antibodies.

The need for the modified TNF-alpha to be biologically inactive only follows from the toxic aspect of the native molecule. And, when blocking the biological effect by modifying the active site, it would be expected that the resulting autoantibodies cannot recognize the native active site and, thus, not be neutralizing. TNF2-1 is an example of such an autoantibody without a neutralizing effect.

The presently claimed invention, however, surprisingly shows that it is possible to modify TNF-alpha in parts of the molecule, such that biologically inactive TNF-alpha may be used to induce neutralizing anti-TNF-alpha antibodies. In Mouritsen, this is neither disclosed nor suggested to be desirable. Further, no one skilled in the art would have expected this to be possible. Mouritsen, therefore, does not teach or suggest the presently claimed invention.

Similarly, other modifications in the human TNF-alpha molecule in accordance with the presently claimed invention have shown how very important it is to select the segments to be modified. Moreover, only in accordance with the presently claimed invention are modified TNF-alpha molecules obtained that (1) are able to induce neutralizing autoantibodies and, at the same time, (2) are devoid of biological activity (due to the replacement of a native segment).

Therefore, Mouritsen would not have led one skilled in the art to the presently claimed invention, notwithstanding allegations to the contrary of record.

As previously argued, it is clear that Mouritsen discloses a general idea of how to modulate unwanted actions of self-proteins, i.e., by using such self-proteins modified by foreign T cell epitopes to induce autoantibodies to the self-proteins. Mouritsen does not, however, teach or suggest the necessity of obtaining neutralizing antibodies or how to obtain them, let alone how to do this as taught in accordance with the presently claimed invention, i.e., by modifying hTNF-alpha only in certain areas of the native hTNF-alpha, so that its neutralizing effect is retained without retaining its toxic biological activity. Thus, the presently claimed invention may be seen as a selection of individual properties and restrictions to be used in connection with the development of effective and

biologically inactive neutralizing autoantibodies to the human TNF-alpha molecule. Such properties and restrictions can only be judged as obvious with hindsight.

Favorable action is requested.

Respectfully submitted,

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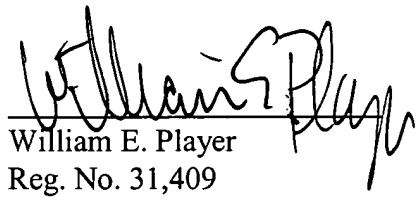
By: 
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